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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,750	12/09/2002	Wilhelm Tischer	HURR-1205	6008

24972 7590 02/21/2006

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,750	TISCHER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,27,33 and 46-94* is/are pending in the application.

4a) Of the above claim(s) *65-69 and 86-94* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,27,33,46-64 and 70-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/9/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *expasy notes*.

DETAILED ACTION

Status of the Application

Claims 1, 27, 33, 46-94 are pending.

Applicant's election with traverse of Group IV, claims 1, 27, 33, 46-64, 70-85 drawn in part to a method for *in vitro* synthesis of deoxyribonucleosides from deoxyribose-1-phosphate (dR1P) and a nucleobase wherein said synthesis is catalyzed by a purine phosphorylase, wherein dR1P is formed from dR5P, wherein dR5P is obtained from condensation of GAP with acetaldehyde, wherein GAP is generated from FDP, and wherein said deoxyribonucleosides are further reacted with a second nucleobase in a reaction catalyzed by a deoxyribosyl transferase (NdT) comprising SEQ ID NO: 14, in a communication filed on 11/3/2005 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 65-68-69 and 86-94 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1, 27, 33, 46-64, 70-85 are at issue and are being examined herein.

Applicants have indicated that claim 44 was canceled and rewritten as claim 93. Applicants also submit that claims 27 and 33 are independent claims. It is noted however that claims 27 and 33 in their current form are dependent upon claims 16 and 32, respectively. Claims 26 and 32 have been canceled in a preliminary amendment. Also, there is no evidence of record of a preliminary amendment where claims 27 and 33 have been rewritten in independent form. Therefore, as of now, these claims are dependent upon canceled claims.

Specification

1. The specification is objected to due to the recitation on page 13, lines 6-8 of "wherein I are percent identity, L is the length of the basic sequence and n is the number of nucleotide or amino acid difference of a sequence to the basic sequence" because as written one cannot determine the intended definition of n. Appropriate correction is required.

Priority

2. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to EUROPEAN PATENT OFFICE (EPO) application number 99 116 425.2 filed on 08/20/1999.

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The foreign priority documents are in English.

4. This application is the US national stage of PCT/EP00/08088 filed on 08/18/2000.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 2/15/2002 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the Examiner.

Claim Objections

6. Claims 49-58, 60-64, 71-74, 79, 81 are objected to as they refer to claim numbers which are no longer applicable as claims 47-95 have been renumbered 46-94 according to 37 CFR 1.126 in view of the fact that there is no claim 46. See page 2 of restriction requirement. Applicant has not updated the new claim numbers in the claims themselves. As a result of this, claims 49, 51-52, 55-56, 60, 62, 64, 71, 79, 81 now depend upon themselves and the remaining claims depend upon claims which were not the intended ones. For examination purposes, the Examiner will assume that the claims have been amended

such that any reference to specific claims has taken into account the renumbering of the claims. For example, while claim 50 now reads "the method of claim 47", the Examiner will interpret the claim to read "the method of claim 46" since previous claim 47 has now been renumbered claim 46. Appropriate correction is required.

7. Claim 85 is objected to due to the recitation of "further reacting said deoxyribonucleoside to synthesize ...of H-phosphonates or phosphoramidites". It appears the term should read "further reacting said deoxyribonucleoside to synthesize ...or H-phosphonates or phosphoramidites". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 27, 33, 46, 48-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 (claims 27, 33, 46, 48-64, 70-85 dependent thereon) is indefinite as it omits essential steps. While the preamble of claim 1 refers to enzymatic synthesis, there is no step where an enzyme is used in the claimed method. Correction is required.

11. Claims 27 and 33 (claims 75-84 dependent thereon) are indefinite as they depend upon canceled claims. For examination purposes, it will be assumed that both claims depend on claim 1. As such, they will be considered duplicates. Correction is required.

12. Claim 46 is indefinite in the recitation of "the method of claim 1, further comprising removing the inorganic phosphate" for the following reasons. Claim 1 already contains a limitation regarding

removing the inorganic phosphate, therefore it is unclear as to how claim 46 further limits claim 1. For examination purposes, claim 46 will be considered a duplicate of claim 1. Correction is required.

13. Claim 54 (claims 57 and 58 dependent thereon) is indefinite in the recitation of "comprising reacting said inorganic phosphate with a saccharide to form a monosaccharide and a phosphorylated monosaccharide" for the following reasons. The term "saccharide" encompasses sugars of different lengths. Thus, the term "saccharide" also encompasses a monosaccharide. Since the claim requires the formation of two products: a monosaccharide and a phosphorylated monosaccharide, it is unclear as to how if the saccharide is a monosaccharide, one can obtain both a monosaccharide and a phosphorylated monosaccharide. At a minimum, the saccharide would have to be a disaccharide. For examination purposes, it will be assumed that the term "saccharide" reads "polysaccharide". Correction is required.

14. Claim 60 is indefinite in the recitation of "comprising isomerizing said deoxyribose 5-phosphate with a deoxyribomutase (EC 2.7.5.1) or a phosphopentose mutase (PPM, EC 5.4.2.7)" for the following reasons. The enzyme corresponding to EC 5.4.2.7 has an official name which is phosphopentomutase and an alternative name which is deoxyribomutase. See attached EXPASy printout. A cursory search of the entry for EC 2.7.5.1 shows that the new EC number for this enzyme is EC 5.4.2.2 which corresponds to a phosphoglucomutase. See attached EXPASy printouts. Therefore, it is unclear as to what is intended by the term "deoxyribomutase (EC 2.7.5.1)". For examination purposes, no patentable weight will be given to the term "deoxyribomutase (EC 2.7.5.1)". Correction is required.

15. Claim 74 is indefinite in the recitation of "*Lactobacilllus*....and is encoded by (a) the nucleotide sequence of ...or (c) a nucleotide sequence hybridizing under stringent conditions to the complementary sequence of (a) or (b)" for the following reasons. As indicated in the sequence listing, SEQ ID NO: 11 corresponds to a nucleic acid from *Salmonella typhi*. Therefore, unless there is evidence that the same nucleic acid can be found in *Lactobacillus leichmannii*, it is unclear as to how the preamble in claim 74 limiting the source of the protein can be applied to item (b). In addition, it is noted that as known in the

art, a nucleic acid sequence is a graphical representation of the order in which nucleotides are arranged in a nucleic acid molecule. Since hybridization occurs among nucleic acid molecules, it is unclear as to how a sequence can hybridize to another sequence. The term "stringent conditions" is also indefinite as it is unclear which polynucleotide is claimed absent a statement of the conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. It is noted that the specification exemplifies several conditions (buffer and temperature) as stringent (page 12, lines 22-26) but has not specifically define what is encompassed by the term "stringent conditions". The term "complementary" is also indefinite as it is unclear if the term encompasses the entire complementary strand, or fragments of any size which are complementary to the target polynucleotide. The specification does not provide a definition of what is encompassed by the term "complementary". For examination purposes, it will be assumed that (1) hybridization occurs among nucleic acids under any hybridization conditions, (2) no patentable weight will be given to the term "*Lactobacillus leichmannii*", (3) the term "complementary sequence of (a) or (b)" reads "complete complement of the nucleic acids of (a) or (b)", and (4) the term "encoded by (a) the nucleotide sequence of SEQ ID NO: 13, (b) a nucleotide sequence encoding the protein...." reads "encoded by (a) the nucleic acid of SEQ ID NO: 13, (b) a nucleic acid encoding the protein....". Correction is required.

16. Claims 75 and 82 are indefinite due to the recitation of "the method of claim 27 (33) wherein the reaction is carried out without isolating intermediate products" in view of the fact that this is exactly the same limitation recited in claim 27 and claim 33. Therefore, it is unclear as to how claims 75 or 82 further limit claim 27 or claim 33. For examination purposes, claims 75 and 82 will be considered as duplicates of claims 27 and 33. Correction is required.

17. Claims 76-81, 83-84 are indefinite as they present limitations regarding claim 27 or claim 33 for which there is no antecedent basis. Claim 76 limits the source of GAP in claim 27 but there is no

reference to GAP in claim 27. Claims 77-78, 80 present limitations regarding step (ii) in claim 27 but there is no step (ii) in claim 27. Claim 81 limits excess starting materials or products in claim 27 but there is no reference to excess starting materials/products in claim 27. Claim 83 refers to step (iii) in claim 27 but there is no step (iii) in claim 27. Claim 84 refers to step (iii) in claim 33 but there is no step (iii) in claim 33. For examination purposes, the limitations recited in claims 76-81 and 83-84 will not be given any patentable weight. As such, claims 76-81 and 83-84 will be considered as duplicates of claims 27 and 33. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1, 27, 33, 46, 48-64, 70-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 27, 33, 46, 48-64, 70-85 are directed to a method to enzymatically produce deoxyribonucleosides *in vitro* wherein the method comprises at a minimum reacting dR1P (deoxyribose-1-phosphate) and a nucleobase. Therefore, the claimed method encompasses any pathway which would lead to the production of a deoxyribonucleoside as long as one of the reactions in the pathway is the conversion of dR1P to a deoxyribonucleoside by any means. It is noted that since there is no indication as to which reaction is catalyzed by an enzyme, or which enzymes are used, there is no limitation as to which steps in the pathway are catalyzed by an enzyme or a chemical catalyst, or how the intermediates in the pathway are produced (i.e., enzymatically or chemical synthesis). As written, the conversion of dR1P

to a deoxyribonucleoside can be made by any enzyme which can catalyze that conversion or by chemical synthesis.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require an extremely large genus of enzymes and catalysts, as well as a genus of methods to produce any intermediate in a pathway that would produce dR1P for which the specification provides no adequate description. While the specification and the art disclose the enzymatic conversion of dR1P to a deoxyribonucleoside with thymidine phosphorylase and purine nucleoside phosphorylase, neither the specification nor the art teach additional enzymes which would catalyze the conversion of dR1P to a deoxyribonucleoside. Furthermore, while the specification discloses the enzymatic synthesis of some precursors of dR1P by using specific enzymes, it provides no information as to the conditions required for chemical synthesis of these precursors, or additional enzymes which would catalyze the synthesis of precursors of dR1P.

Even if the claims were to be limited such that all the steps in a pathway which would result in the synthesis of deoxyribonucleosides are enzyme-catalyzed, the claims require a genus of enzymes which is structurally unrelated. A sufficient written description of a genus of enzymes may be achieved by a recitation of a representative number of enzymes defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of enzymes required in the claimed method, and there is no information as to a correlation between the structures disclosed/known in the art and their required enzymatic activity. Furthermore, while one could argue that the structures of known thymidine phosphorylases, purine nucleoside phosphorylases, phosphopentose mutases, phosphopentose aldolases, fructose diphosphate aldolases I and II, and nucleoside 2-deoxyribosyl transferases are representative of all members of the genus of enzymes required, such that the claimed invention is adequately described, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with the enzymatic activities required has been provided, one cannot reasonably conclude that the known structures are representative of all the enzymes required in the claimed invention.

Due to the fact that the specification only discloses (1) the enzymatic synthesis of deoxyribonucleosides, and (2) a single species of each of the enzymes required, as well as the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill

in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

20. Claims 1, 27, 33, 46, 48-64, 70-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in vitro* enzymatic synthesis of deoxyribonucleosides wherein said method comprises reacting deoxyribose 1-phosphate (dR1P) and a nucleobase in the presence of a thymidine phosphorylase, or a purine nucleoside phosphorylase, does not reasonably provide enablement for a method for the production of deoxyribonucleosides wherein said method requires reacting dR1P and a nucleobase in the presence of any enzyme and/or under any conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1, 27, 33, 46, 48-64, 70-85 are so broad as to encompass a method for the production of deoxyribonucleosides wherein said method requires reacting dR1P and a nucleobase in the presence of any enzyme and/or under any conditions (i.e., non-enzymatic). As indicated above, the "enzymatic" limitation does not necessarily apply to the reaction of dR1P with a nucleobase as the claims as written do not require that reaction to be catalyzed by an enzyme. See written description rejection above for discussion of scope. The claimed method encompasses any pathway

which would lead to the production of a deoxyribonucleoside as long as one of the reactions in the pathway is the reaction of dR1P with a nucleobase to produce a deoxyribonucleoside by any means. As written, the conversion of dR1P to a deoxyribonucleoside can be made by any enzyme which can catalyze that conversion, or under unknowns conditions which would lead to the required reaction to take place. The enablement provided is not commensurate in scope with the claims due to the extremely large number of unknown enzymes required in the claimed invention, and/or the extremely large number of unknown conditions which would allow the reaction between dR1P and a nucleobase to produce a deoxyribonucleoside. In the instant case, the specification enables the production of deoxyribonucleosides by reacting dR1P and a nucleobase in the presence of a thymidine phosphorylase, or a purine nucleoside phosphorylase.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the synthesis of deoxyadenosine by using *E. coli* purine nucleoside phosphorylase (PNP) to catalyze the reaction of dR1P with a nucleobase, wherein dR1P was enzymatically produced from dR5P, and wherein dR5P was enzymatically produced from fructose 1,6-bisphosphate, as a working example. However, the specification fails to disclose (1) other enzymes (or their structures) which would catalyze the required reaction, and/or (2) conditions which would not require an enzyme that would allow the reaction between dR1P and a nucleobase to produce a deoxynucleoside.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and the ability to catalyze the reaction between dR1P and a nucleobase to produce a deoxyribonucleoside such that one of skill in the art can envision the structure of any enzyme having the ability to catalyze that reaction. In addition, the art does not provide any teaching or guidance as to how the structures of those enzymes which are known in the art correlate with the ability to catalyze

the reaction between dR1P and a nucleobase. The art clearly teaches that structural changes in a protein to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a protein were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all enzymes which can catalyze the reaction between dR1P and a nucleobase, or all the conditions which would allow the reaction between dR1P and a nucleobase to produce a deoxynucleoside. In the absence of (1) a correlation between structure and the required enzymatic activity, and/or (2) some guidance as to which conditions/catalysts would allow the required reaction to take place, one of skill in the art would have to test an essentially infinite number of proteins to determine (1) which ones have the desired enzymatic activity, and/or (2) which conditions (non-enzymatic) would allow the required reaction to occur.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1, 27, 33, 46-49, 75-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi et al. (EP 0411158 B1, published on May 29, 1996; cited in the IDS and the previous Office Action) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997). Yamauchi et al. teach a process for the production of deoxyribonucleosides by using purine nucleoside phosphorylases from

Bacillus stearothermophilus (page 3, lines 31-34; page 7, lines 5-49) which catalyze the reaction of 2-deoxyribose-1-phosphate (page 10, lines 18-20) with nucleobases such as adenine, guanine, hypoxanthine, xanthine, cytosine, uracil, thymine, and 6-azauracil (page 9, line 53-page 10, line 10). There are no intermediate products disclosed by Yamauchi et al. in the reaction between the dR1P and the nucleobase. While Yamauchi et al. teach separation and purification of the deoxyribonucleoside by several chromatographic methods, extraction, partition between two liquid phases, gel filtration, and methods which use difference in solubility (page 10, lines 49-53), Yamauchi et al. do not specifically teach the removal of inorganic phosphate. Baranov et al. teach a method for obtaining polypeptides in a cell-free system and teach the removal of inorganic phosphate and inorganic pyrophosphate from the system to allow the continuous production of the desired product (page 2, second column, lines 11-26). Baranov et al. do not teach a method for the production of deoxyribonucleosides.

Claims 1, 27, 33, 46, 47, 75-84 as interpreted are directed in part to a method for the production of deoyribonucleosides wherein said method requires reacting deoxyribose-1-phosphate (dR1P) and a nucleobase, wherein said reaction produces a deoxyribonucleoside and inorganic phosphate, wherein the inorganic phosphate is removed, and wherein the intermediate products are not isolated. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. Claims 48-49 are directed in part to the method of claim 1 wherein the nucleobase is either thymine, uracil, adenosine, guanine, hypoxanthine, or 6-azauracil.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to remove the inorganic phosphate, as taught by Baranov et al., which results from the synthesis of deoxyribonucleosides, as taught by Yamauchi et al. A person of ordinary skill in the art is motivated to remove inorganic phosphate for the benefit of driving the reaction between dR1P and the nucleobase towards synthesis of the deoxyribonucleoside. One of ordinary skill in the art has a reasonable expectation of success at removing inorganic phosphate since removal of inorganic phosphate is well known in the art

and disclosed by Baranov et al. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

24. Claims 1, 27, 33, 46-48, 59-64, 75-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, C. (Ph.D. Thesis,Texas A&M University, 1989; cited in the specification) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997). Barbas, as admitted in the specification (page 2, lines 8-24), teaches the synthesis of deoxyribonucleosides wherein dR1P and a nucleobase are combined in a reaction catalyzed by thymidine phosphorylase and wherein dR1P is produced by isomerizing dR5P in a reaction catalyzed by phosphopentosemutase (pages 48-53; Scheme III in page 58). The nucleobase in Scheme III is thymidine. Barbas also teaches the cloning and production of fructose 1,6-biphosphate aldolase from *C. glutamicum* and *E. coli* (pages 70-84) and discloses the use of aldolases in the synthesis of useful compounds as well as the combined use of aldolases and isomerases for the production of unusual sugars (pages 64-67; Figure 25). Barbas teaches the production of 2-deoxyribose-5-phosphate from GAP and acetaldehyde in a reaction catalyzed by a deoxyribose-5-phosphate aldolase (page 88, second paragraph). Barbas does not teach removal of inorganic phosphate formed in a reaction between dR1P and a nucleobase. Baranov et al. teach a method for obtaining polypeptides in a cell-free system and teach the removal of inorganic phosphate and inorganic pyrophosphate from the system to allow the continuous production of the desired product (page 2, second column, lines 11-26). Baranov et al. do not teach a method for the production of deoxyribonucleosides.

Claims 1, 27, 33, 46, 47, 75-84 as interpreted are directed in part to a method for the production of deoyribonucleosides wherein said method requires reacting deoxyribose-1-phosphate (dR1P) and a nucleobase, wherein said reaction produces a deoxyribonucleoside and inorganic phosphate, wherein the inorganic phosphate is removed, and wherein the intermediate products are not isolated. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. Claim 48 is directed in part to

the method of claim 1 wherein the nucleobase is either thymine, uracil, adenosine, guanine, hypoxanthine, or an analog thereof. Claims 59-64 are directed in part to a method for the production of deoyribonucleosides wherein said method requires reacting deoxyribose-1-phosphate (dR1P) and a nucleobase, wherein said reaction produces a deoxyribonucleoside and inorganic phosphate, wherein the inorganic phosphate is removed, wherein dR1P is generated by isomerizing deoxyribose-5-phosphate (dR5P) with a deoxyribomutase or a phosphopentose mutase, wherein dR5P is formed by condensing glyceraldehyde-3-phosphate (GAP) with acetaldehyde prior to isomerization in the presence of phosphopentose aldolase, and wherein GAP is enzymatically generated from fructose-1,6,diphosphate in a reaction catalyzed by an FDP-aldolase I or and FDP-aldolase II.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to remove the inorganic phosphate, as taught by Baranov et al., which results from the synthesis of deoxyribonucleosides, as taught by Barbas. Also, while not explicitly taught by Barbas as a single method, it would have been obvious to (1) produce dR5P by condensation of GAP and acetaldehyde, wherein said condensation is catalyzed by a phosphopentose mutase prior to its use to produce a deoxyribonucleoside, and (2) generate GAP in a reaction catalyzed by an FDP (fructose diphosphate) aldolase. A person of ordinary skill in the art is motivated to (1) remove inorganic phosphate for the benefit of driving the reaction between dR1P and the nucleobase towards synthesis of the deoxyribonucleoside, and (2) produce the precursors of dR1P (dR5P and GAP) enzymatically since it is well known in the art that enzymatic processes are more specific in regard to the substrates and products, therefore having the potential of being more efficient than chemical synthesis. One of ordinary skill in the art has a reasonable expectation of success at removing inorganic phosphate and producing the dR1P precursors enzymatically since removal of inorganic phosphate is well known in the art and the enzymatic synthesis of dR5P and GAP is disclosed by Barbas. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

25. Claims 50 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, C. (Ph.D. Thesis,Texas A&M University, 1989; cited in the specification) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997), and further in view of DeFrees et al. (WO 96/32491 published 10/17/1996). The teachings of Barbas and Baranov et al. have been discussed above. Barbas does not teach removal of inorganic phosphate by (1) precipitation or (2) conversion of inorganic phosphate into inorganic pyrophosphate followed by precipitation of the inorganic pyrophosphate. Baranov et al. do not teach a method for the production of deoxyribonucleosides or precipitation of inorganic phosphate/inorganic pyrophosphate. DeFrees et al. teach the enzymatic synthesis of glycosidic linkages and teach that inorganic pyrophosphate is a byproduct of the preparation of CMP-NeuAc and should be removed to avoid inhibition of other enzymes. DeFrees et al. also teach that inorganic pyrophosphate as well as inorganic phosphate can form a precipitate of low solubility with divalent metal cations, therefore allowing removal of inorganic pyrophosphate and inorganic phosphate (page 11, lines 11-28). DeFrees et al. do not teach a method for the production of deoxyribonucleosides or the conversion of inorganic phosphate to inorganic pyrophosphate.

Claim 50 is directed in part to a method for the production of deoyribonucleosides wherein said method requires reacting deoxyribose-1-phosphate (dR1P) and a nucleobase, wherein said reaction produces a deoxyribonucleoside and inorganic phosphate, wherein the inorganic phosphate is removed, and wherein said inorganic phosphate is removed by converting said inorganic phosphate to inorganic pyrophosphate or by precipitation. Claim 53 is directed to the method of claim 50 wherein the inorganic pyrophosphate is removed by precipitation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to remove inorganic phosphate, as taught by Baranov et al., which results from the synthesis of deoxyribonucleosides, as taught by Barbas, by precipitating inorganic phosphate, as taught by DeFrees et

al. Also, it would have been obvious to remove inorganic phosphate by converting it to inorganic pyrophosphate and then precipitating inorganic pyrophosphate. A person of ordinary skill in the art is motivated to (1) remove inorganic phosphate for the benefit of driving the reaction between dR1P and the nucleobase towards synthesis of the product, (2) remove inorganic phosphate by converting inorganic phosphate into inorganic pyrophosphate for the benefit of enzymatically removing inorganic phosphate since several enzymes are known to catalyze a reaction where inorganic phosphate is converted into pyrophosphate, and (3) use precipitation as the method of removal of inorganic phosphate/inorganic pyrophosphate as DeFrees et al. teach that both can be complexed with divalent cations for precipitation. One of ordinary skill in the art has a reasonable expectation of success at removing inorganic phosphate/inorganic pyrophosphate by precipitation since DeFrees et al. teach the precipitation of both compounds. Also, one of ordinary skill in the art has a reasonable expectation of success at converting inorganic phosphate into inorganic pyrophosphate as several enzymes are known to accomplish that conversion (e.g., inorganic pyrophosphatase). Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

It is noted that claims 51-52, 54-58 have not been rejected as obvious over the teachings of Barbas in view of Baranov et al. as the Examiner has not been able to find prior art which would provide a motivation to remove inorganic phosphate by reacting inorganic phosphate with fructose diphosphate, or by reacting inorganic phosphate with a polysaccharide.

26. Claims 50 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi et al. (EP 0411158 B1, published on May 29, 1996; cited in the IDS and the previous Office Action) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997), and further in view of DeFrees et al. (WO 96/32491 published 10/17/1996). The teachings of Yamauchi et al. and Baranov et al. have been discussed above. Yamauchi et al. do not teach removal of inorganic phosphate by (1) precipitation or (2)

conversion of inorganic phosphate into inorganic pyrophosphate followed by precipitation of the inorganic pyrophosphate. Baranov et al. do not teach a method for the production of deoxyribonucleosides or precipitation of inorganic phosphate/inorganic pyrophosphate. DeFrees et al. teach the enzymatic synthesis of glycosidic linkages and teach that inorganic pyrophosphate is a byproduct of the preparation of CMP-NeuAc and should be removed to avoid inhibition of other enzymes. DeFrees et al. also teach that inorganic pyrophosphate as well as inorganic phosphate can form a precipitate of low solubility with divalent metal cations, therefore allowing removal of inorganic pyrophosphate and inorganic phosphate (page 11, lines 11-28). DeFrees et al. do not teach a method for the production of deoxyribonucleosides or the conversion of inorganic phosphate to inorganic pyrophosphate.

Claim 50 is directed in part to a method for the production of deoyribonucleosides wherein said method requires reacting deoxyribose-1-phosphate (dR1P) and a nucleobase, wherein said reaction produces a deoxyribonucleoside and inorganic phosphate, wherein the inorganic phosphate is removed, and wherein said inorganic phosphate is removed by converting said inorganic phosphate to inorganic pyrophosphate or by precipitation. Claim 53 is directed to the method of claim 50 wherein the inorganic pyrophosphate is removed by precipitation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to remove inorganic phosphate, as taught by Baranov et al., which results from the synthesis of deoxyribonucleosides, as taught by Yamauchi et al., by precipitating inorganic phosphate, as taught by DeFrees et al. Also, it would have been obvious to remove inorganic phosphate by converting it to inorganic pyrophosphate and then precipitating inorganic pyrophosphate. A person of ordinary skill in the art is motivated to (1) remove inorganic phosphate for the benefit of driving the reaction between dR1P and the nucleobase towards synthesis of the product, (2) remove inorganic phosphate by converting inorganic phosphate into inorganic pyrophosphate for the benefit of enzymatically removing inorganic

phosphate since several enzymes are known to catalyze a reaction where inorganic phosphate is converted into pyrophosphate, and (3) use precipitation as the method of removal of inorganic phosphate/inorganic pyrophosphate as DeFrees et al. teach that both can be complexed with divalent cations for precipitation. One of ordinary skill in the art has a reasonable expectation of success at removing inorganic phosphate/inorganic pyrophosphate by precipitation since DeFrees et al. teach the precipitation of both compounds. Also, one of ordinary skill in the art has a reasonable expectation of success at converting inorganic phosphate into inorganic pyrophosphate as several enzymes are known to accomplish that conversion (e.g., inorganic pyrophosphatase). Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

It is noted that claims 51-52, 54-58 have not been rejected as obvious over the teachings of Yamauchi et al. in view of Baranov et al. as the Examiner has not been able to find prior art which would provide a motivation to remove inorganic phosphate by reacting inorganic phosphate with fructose diphosphate, or by reacting inorganic phosphate with a polysaccharide.

Conclusion

27. No claim is in condition for allowance.

28. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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Art Unit 1652

DR
February 13, 2006